(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07049 A2

(51) International Patent Classification[7]: A61K 31/445

(21) International Application Number: PCT/EP00/07030

(22) International Filing Date: 21 July 2000 (21.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99114508.7 23 July 1999 (23.07.1999) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07049 A2

(54) Title: OPHTHALMIC COMPOSITION

(57) Abstract: The present invention is related to an ophthalmic composition comprising ketotifen as a pharmaceutically active agent.

Ophthalmic Composition

This invention is directed to an ophthalmic composition comprising ketotifen as a pharmaceutically active agent.

An ophthalmic composition comprising ketotifen fumarate is already known, and already on the market. The composition of the present invention is superior compared to the known compositions in that it has a substantially lower dosage of the pharmaceutically active agent. In result said composition combines a high efficacy with a better tolerability. A further surprising advantage of the composition as disclosed herein is seen in the fact that said composition can be sterilized without any significant decomposition of the pharmaceutically active agent, or other components of the composition.

The composition of the present invention comprises a ketotifen salt, in a concentration of 0.01 to 0.04 %, a non-ionic tonicity agent in an amount such that the total tonicity of the composition has an osmolarity in the range of 210 to 290 milliosmoles, optionally a preservative, acid or base for bringing the pH to weak acidity, and water.

The ketotifen salt is preferably ketotifen fumarate. The concentration of the ketotifen salt is preferably 0.03 to 0.04 %, even more preferred 0.025 %. The non-ionic tonicity agent is preferably glycerol. The non-ionic tonicity agent is preferably present in an amount such that the total tonicity of the composition has an osmolarity in the range of 230 to 260 milli-osmoles, more preferred to 235 to 255 milliosmoles. If glycerol is used, the concentration of glycerol is preferably in the range of 1.5 to 2.5 %. A preservative is present for multi-dose units, but it is routinely not present in single dose units. If a preservative is present, the preferred preservative is benzalkonium chloride. Typically the amount of the preservative is 0.005 to 0.02 %, more preferred 0.01 %. An acid or base is used in small amounts, such as 0.05 to 0.1 %, for adjusting the pH, preferred is the use of small amounts of sodium hydroxide 1N, e.g. 0.075 % of such solution. The pH of the composition is adjusted to weak acidity for optimization of stability and tolerabilty, and said pH of weak acidity is understood to mean preferably a pH of 4.4 to 5.8, more preferably a pH of 5 to 5.5, and most preferably a pH of 5.3. The water present in the composition is typically water for injection.

A preferred composition of this invention comprises ketotifen fumarate, in a concentration of 0.03 to 0.04 %, glycerol in a concentration of 2 to 2.5 %, optionally benzalkonium chloride in an amount of 0.005 to 0.02 %, sodium hydroxide, and water. An even more preferred composition comprises ketotifen fumarate, in a concentration of 0.025 %, glycerol in a concentration of 2.125 %, optionally benzalkonium chloride in an amount of 0.01 %, sodium hydroxide, and water.

The ophthalmic composition of this invention is useful as eye drops, whether as a preserved multi dose unit, or as an unpreserved single dose unit. Said eye drops do have a high therapeutic value because they can be used for the treatment and the temporary prevention of itching of the eye due to allergic conjunctivitis, and they can be used for the treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis.

Despite the low concentration of the pharmaceutically active ingredient, ketotifen fumarate, the recommended dosage is lower than for known ketotifen fumarate preparations. Thus, one drop of the composition of this invention should be applied advantageously two times per day, in contrast to 1 to 2 drops four times a day of the prior art compositions. The fact that the composition of this invention can be applied with an overall very low level of pharmaceutically active ingredient, especially ketotifen fumarate, is one of the surprising findings in the context of this invention. A further finding is that a stabilizer such as for example sodium edetate might be omitted.

Said ophthalmic composition can be manufactured by mixing the ingredients, and packaging the resulting mixture, both as known in the art. Sterilization of the composition and the primary package can be effected e.g. by gamma irradiation, by ethyleneoxide treatment, by electron beam, by autoclaving or by steam sterilization.

Example 1: Multidose Units:

Ketotifen fumarate	0.25 mg (0.025 %)
Benzalkonium chloride	0.10 mg (0.010 %)
Glycerol 100 %	21.25 mg (2.125 %)
Sodium hydroxide 1N	about 0.75 mg (~ 0.075 %)
Water for injection ad	ad 1.0 ml

Example 2: Single dose Units:

Ketotifen fumarate	0.25 mg (0.025 %)
Glycerol 100 %	21.25 mg (2.125 %)
Sodium hydroxide 1N	about 0.75 mg (~ 0.075 %)
Water for injection ad	ad 1.0 ml

Claims

1. An ophthalmic composition comprising a ketotifen salt, in a concentration of 0.01 to 0.04 %, a non-ionic tonicity agent in an amount such that the total tonicity of the composition has an osmolarity in the range of 210 to 290 milliosmoles, optionally a preservative, acid or base for bringing the pH to weak acidity, and water.

2. The composition of claim 1 wherein the ketotifen salt is ketotifen fumarate.

3. The composition of claim 1 wherein the concentration of the ketotifen salt is 0.03 to 0.04 %, preferably 0.025 %.

4. The composition of claim 1 wherein the non-ionic tonicity agent is glycerol.

5. The composition of claim 1 wherein the non-ionic tonicity agent is glycerol in an amount of 1.5 to 2.5 %.

6. The composition of claim 1 wherein the preservative is benzalkonium chloride.

7. The composition of claim 1 wherein the preservative is absent.

8. The composition of claim 1 which comprises ketotifen fumarate, in a concentration of 0.03 to 0.04 %, glycerol in a concentration of 2 to 2.5 %, optionally benzalkonium chloride in an amount of 0.005 to 0.02 %, sodium hydroxide, and water.

9. The composition of claim 1 which comprises

Ketotifen fumarate	0.25 mg (0.025 %),
Benzalkonium chloride	0.10 mg (0.010 %),
Glycerol 100 %	21.25 mg (2.125 %),
Sodium hydroxide 1N	about 0.75 mg (~ 0.075 %),
Water for injection ad	ad 1.0 ml.

10. The composition of claim 1 which comprises

Ketotifen fumarate	0.25 mg (0.025 %),
Glycerol 100 %	21.25 mg (2.125 %),
Sodium hydroxide 1N	about 0.75 mg (~ 0.075 %),
Water for injection ad	ad 1.0 ml.